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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/551,704

01/22/2007

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EXAMINER

BELYAVSKYI, MICHAEL A

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/551,704	Applicant(s) PALEFSKY ET AL.	
	Examiner Michail A. Belyavskyi	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-26 and 28-34 is/are pending in the application.
- 4a) Of the above claim(s) 28-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01/22/07 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1644

DETAILED ACTION

1 Applicant's amendment, filed 07/11/08 is acknowledged.

Claims 22-26 and 28-34 are pending.

Applicant's election without traverse of Group V, claims 22-26 in the reply filed on 07/11/08 is acknowledged.

2. Claims 28-34 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 22-26 read on a composition comprising a mutant human S1008 protein that is at least 95% identical to SEQ ID NO:2 are under consideration in the instant application.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is indefinite and ambiguous in the recitation of S100A8 protein. Recitation of a protein without providing SEQ ID NO for the protein is indefinite and ambiguous because different laboratories may have the same name for a different proteins.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a human S100A8 protein of SEQ ID NO:2 and a specific mutant form of said human S100A8 protein wherein said mutation is a

Art Unit: 1644

substitution of cysteine at residue 42 with an alanine does not reasonably provide enablement for a composition comprising any mutant human S100A8 protein that is at least 95% identical to SEQ ID NO:2.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The claims as written encompass the genus of peptide and polypeptide amino acid sequences. The genus encompasses peptides wherein such peptides have numerous differences in amino acid sequences.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Applicant discloses a specific calcium binding human S100A8 protein of SEQ ID NO:2 and specific mutation of said protein, wherein a cysteine at residue 42 has been replaced with an alanine. (see entire specification, page 18 in particular). The specification disclosed that overall structure and function of S100A8 was not destroyed by said mutation, however, said mutant protein was unable to form a covalently-bound homodimer and conferring oxidation resistance to said protein (see overlapping pages 18 and 19 in particular). Applicant has not taught how to make and/or use any mutant human S100A8 protein that is at least 95% identical to SEQ ID NO:2. The structural characteristics of said human S100A8 protein of SEQ ID NO:2 that are essential for the function of said protein are not defined in the specification or claims.

Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993.

Art Unit: 1644

90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular). Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" residue at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Even single amino acid differences can result in drastically altered functions between two proteins. For example, Wang et al. (JBC, 2001 276:49213-49220) show that a single amino acid determines lysophospholipid specificity of the S1P1 (EDG1) and LPA1 (EDG2) phospholipids growth factor receptors (e.g., abstract). Wang et al shows that a single amino acid Glu¹²¹ in S1P1/EDG1, which corresponds to Gln¹²⁵ in LPA1/EDG2, influences the specificity for S1P or LAP (see page 49213 last ¶). Mutating the Arg-Glu-Gly motif to that is conserved among LPA receptors Arg-Gln-Gly, lead to ligand selectivity switch in concert with the mutations. Moreover, Whisstock et al (Quarterly Review of Biophysics, 2003, 36, pp307-340) teaches that prediction of protein function from sequence and structure is difficult problem, because homologous proteins often have different function. A fundamental problem is that function is in many cases an ill-defined concept (see Abstract in particular). Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions.

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of this unpredictability; the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity *over the full length of SEQ ID NO:2* or very specific replacement of cysteine at residue 42 with an alanine, to *share the same function* as the human S100A8 protein.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed composition comprising any mutant human S100A8 protein that is at least 95% identical to SEQ ID NO:2 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Art Unit: 1644

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 22- 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent 5,731,166 or US Patent 5,776,348 or US Patent 6,620,790 or US Patent 7,081,345 each in view of view of Harrison et al (J of Bio. Chem, 1999, v.274, pages 8561-8569.

US Patent '166 teaches a composition comprising a protein of SEQ ID NO: 7 or a mutant form of said protein. It is noted that the referenced protein is 100% identical to the claimed SEQ ID NO:2. (see, entire document, Abstract, column 6 and sequence alignment).

US Patent '348 teaches a composition comprising a protein of SEQ ID NO: 1 or a mutant form of said protein. It is noted that the referenced protein is 100% identical to the claimed SEQ ID NO:2. (see, entire document, Abstract, columns 15 and 16 and sequence alignment).

US Patent '790 teaches a composition comprising a protein of SEQ ID NO: 2 or a mutant form of said protein. It is noted that the referenced protein is 100% identical to the claimed SEQ ID NO:2. (see, entire document, Abstract, column 4 and 5 and sequence alignment).

US Patent '345 teaches a composition comprising a protein of SEQ ID NO: 22 or a mutant form of said protein. It is noted that the referenced protein is 100% identical to the claimed SEQ ID NO:2. (see, entire document, Abstract, columns 4, 6 and sequence alignment).

Art Unit: 1644

It is noted that US Patent 5,731,166 or US Patent 5,776,348 or US Patent 6,620,790 or US Patent 7,081,345 does not explicitly teach a specific mutant form of disclosed proteins comprising replacement of cysteine at residue 42 with an alanine.

Harrison et al., teach a murine S100A8 protein, wherein cysteine at residue 42 is replaced with an alanine (see entire document, Abstract in particular). Harrison et al., teach that said specific mutation results in conferring oxidation resistance to said protein (see page 8566 in particular).

All the claimed elements were known in the prior art and one skill in the art could have combined the elements as claimed by known methods with no change in their respective function and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc.*, 550 U.S., 82 USPQ2d 1385, 2007).

Thus it would have been obvious to one of the ordinary skill in the art at the time the invention was made to replace cysteine at residue 42 with alanine with a reasonable expectation of success because the prior art suggests that said substitution would confer oxidation resistance to said protein.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskiy whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571/272-0878.

The fax number for the organization where this application or proceeding is assigned is 571/273-8300.

Art Unit: 1644

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michail A Belyavskyi/
Primary Examiner, Art Unit 1644